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Descripti n

The present invention relates to a process for the preparation of pharmaceutical tablets in whlch the active agent can be liberated from the tablet at a controlled speed and which speed of liberation can be set at the same level from batch to batch.

When a pharmaceutical substance is administered orally, it may have detrimental side effects. The occurrence of these side effects can often be reduced by physical means by bringing the preparation into such a form from which the active agent is liberated more slowly than normally. The active agent may irritate the alimentary canal locally when high concentrations of the active agent come into contact with the intenstinal walls. In such cases, when the liberation of the active agent from the preparation is controlled so that its absorption into the system and its liberation from the preparation are in correct proportion, the irritating effect can often be avoided.

Moreover, there are cases in which the effect of the active agent is of such a short duration that the interval of administration necessary to maintain the correct concentration of active agent becomes inconveniently short, from the point of view of the patient, which again tends to cause unevenness of administration and forgetfulness about taking the medicine. Such a situation can also be made easier by means of a preparation form that has a higher quantity of active agent but retarded liberation.

There are many methods for the preparation of orally administered medicines that liberate the active agent slowly, by physical means.

It is possible to prepare grains that are coated with a film retarding the liberation of the active agent. From such grains it is possible to press tablets, or the grains may be packed in dose units into gelatin capsules. The method may also be considered as included in this group in which the entire tablet is coated with the film mentioned above.

According to another method, a so-called matrix tablet is prepared in which the active agent and the auxiliary agents are together with the agent/agents controllIng the liberation, pressed into a uniform network or pore structure or frame from which the active agent is liberated slowly. Such a "network structure" can also be formed after compression, e.g. by means of heat treatment, when substances already in the composition melt or become softer at the temperature used.

Although pharmaceutical preparations with controlled liberation of the active agent have proved highly important in practice, their use as a rule involves the drawback that the rate of liberation of the active agent vari s and may be significantly differ nt in differ nt batch s of preparation. This can result in serious detrimental effects. As attempts are made, by means of slow liberation, to prevent irritation of the intestinal wall, e.g. by high local concentrations, variations in the rate of liberation may cause two types of drawbacks. If the rat of liberation is higher than intended, the irritation cannot be eliminated adequat ly. On the other hand, if th rat of liberation is low r than intended, sufficiently high concentrations of active agent are not reached in the organism for the desired response to treatment.

When the aim of controlled liberation is, e.g., longer intervals of administration or the elimination of excessively high local concentrations of active agent in the organism, risks are also produced if there are variations in the liberation of the active agent. A liberation slower than Intended may even cause occurrence of detrimental side effects. However, the risk may also be increased if the rate of liberation becomes very high, for in preparations of this type the quantity of active agent is often larger than in ordinary tablets.

In order to avoid the above drawbacks, attempts have been made to adjust the rate of liberation of the active agent to the appropriate level e.g., by determining the compression force considered to be appropriate at the beginning of the tablet formation. This is, however, inadequate for during the tablet production the compression force may vary out of many reasons, resulting in batch-internal variations in the rate of liberation, and these are not easy to control. Another way is to control the batches carefully afterwards and to reject the unacceptable batches. This is again an operation that involves expense.

The present invention provides a process for the preparation of matrix-type tablets with retarded liberation of the active agent in which the liberation of the active agent takes place at a predetermined speed from a polymethacrylate matrix, characterized in that the retarding matrix substance used in the granulation process comprises at least 8.75 wt. %, based on the gross weight of the tablets, of a methacrylate polymer insoluble in neutral or slightly acid water, either as a solution in an organic solvent or as a dispersion in water and that, before the tablets are compressed, an ester of a high molecular weight fatty acid or a derivative thereof produced by hydrogenation is mixed into the grain mix as a controlling agent in an amount (within the range 1—30% by weight based on the gross tablet weight) calculated to provide a determined rate of release of the active agent which is independent of the tablet compression pressure.

The retarded liberation of the actlve agent is produced by means of a so-called matrix method in which previously known polymethacrylate plastics, which have also been used for this purpose earlier, are used as formers of the retarding matrix.

In a preferred process in accordance with the Invention the drug, i.e. the active agent, with its auxiliary agents is granulated by means of a water dispersion or a solution of a polymethacrylate Insoluble in water at pH 7.0 or less, in

which solution the polymer has been dissolved into organic solvents such as halogenated hydrocarbons, preferably methylenechloride, acetone, alcohols, or mixtures of same. According to studies which have been carried out in the case of active agents highly dissociative in water, it is advantageous to use a solution of polymethacrylate in an organic solvent, because then the water dispersion tends to decompose and an effect of inhibition of dissolution is not produced with reasonably low quantities of polymer. Suitable polymethacrylate plastic is a copolymerizate of acrylic and methacrylic acid esters containing quarternary ammonium groups, or a copolymerizate of methacrylic acid and methylester of methacrylic acid with anionic character. It is also possible to use a water dispersion of a copolymerizate of methyl and ethyl esters of acrylic and methacrylic acid with neutral character.

Polymethacrylate plastics usuable in the process are available, e.g. under the following names:

Eudragit RS
Eudragit RL
Eudragit E 30 D (30% water dispersion)
Eudragit S
Eudragit L (Eudragit is a registered Trade Mark).

The granulation proper may be performed by means of known processes and equipment used in the preparation of the tablet mix. The substances can then be moistened with a solution or dispersion of the polymer, screened into a grain form of appropriate size, and dried, or they may be granulated by spraying with a solution or dispersion in a so-called hover-layer apparatus or in fluidized bed apparatus. The preferred proportion of methacrylate polymer is 8.6 to 21.8 wt.% of the total composition.

When tablets are pressed from such grains, it has been noticed that the liberation of the active agent from them is almost independent from the compression force used in making them, which force, as a rule in tablets of the matrix type prepared by means of other processes, has a considerable effect on the rate of liberation. This property is important, because changes in the compression pressure occurring during the tablet formation in the production cannot produce non-homogeneity in the tablets.

In order to control the rate of liberation of the active agent to the desired level, in the process in accordance with the present invention particular controlling agents are used in the tablets pressed out of the grains produced in the way described above. When substances best suitable for this purpose were being looked for, it was noticed that a prerequisite for their usability was, besides correlati n between their quantity and rat of liberation of the active agent, that the controlling effect was present with low quantities of controlling agent. By using low quantities it is possible to avoid variations in welght and size of tablet which is unavoidable when using larger quantities of controlling agents in different tablet batches. The quantities used are usually at a maximum 30% preferably less than 15%, from the gross weight of the tablet. Particularly suitable substances are certain esters of large-molecule fatty acids which can be brought into a powdery state and which either occur in nature or may be obtained from substances occurring in nature by means of hydrogenation, such as waxes and hydrogenated fats. The saturated large-molecule fatty acid esters include glycerides of acids of the formula $CH_3—(CH_2)_{10-22}—COOH$ and $CH_3—(CH_2)_{9-29}—OH$ esters of the same acids and of large-molecule alcohols. Also, it is possible to use derivatives of unsaturated fatty acids or of their hydrogenated derivatives which contain the same number of carbon atoms. Among suitable commercial products should be mentioned Cutina ®HR, which is hydrogenated castor oil, and Sterotex ®, which is hydrogenated cotton seed oil.

The controlling agents can be added before compression of the tablets in the powdery form to the ready-dried grains by simply stirring. Having the nature of lipids, in the spaces between th grains they control the penetration of water into the network structure of the matrix and thereby affect the rate of dissolution of the active agent. When used in suitable concentrations, the effect is in direct proportion to the quantity of the substances.

Thus, the formulation must be made to includ in each particular case an appropriate quantity of a controlling agent, preferably in powdery form, whereby it is, by means of minor changes in the concentration of said agent before tablet formation, possible by means of calculation to adjust the final and precise rate of liberation of the activ agent from the tablets.

An additional advantage of the use of the controlling agent in accordance with the invention is that the flow of the grains in the machine is improved and troubles of compression pressure and distribution, if any, are also eliminated. It is important further that the independence of th rate of liberation of the active agent from changes in the compression pressure, mentioned above, is retained in spite of the employment of the controlling agents.

The following examples illustrate the invention more closely without, however, restricting its scope:

Example 1

Quinidine tablets

Chinidin. bisulf. (anhydrous) equivalent of quinidine sulphate	200 mg
Macrogol. 6000	20 mg
Talc.	3 mg
Eudragit E 30 D (water dispersion)	150 mg
Cutina HR	q.s.

Th quinidine bisulphate, macrogol. 6000, and the talc were mixed tog ther. The mixture was granulated by means of Eudragit E 30 D (water dispersion), and the grains were dried.

Into the dry grain mix, th Cutina HR in powdery form was mixed. The mix was tabletted to 11...12kg (Pfizer apparatus) strength in a way in itself known.

Out of the tablets, the dissolution (liberation) of the active agent into water during 1 hour was determined as a function of the quantity of the controlling agent (Cutina HR). A linear relationship was found as shown in Fig. 1 of the accompanying drawings.

In another experiment, the compression of the tablets was performed out of the same mix but by using different compression pressures, whereupon the dissolution of the active agent into water during 1 hour was determined as a function of the compression pressure. The result is shown in Fig. 2 of the drawings. As the dissolution apparatus was used the apparatus described in Pharmacopoea Nordica and in USP, and as the dissolving liquid was used water.

Analogous with the process described in Example 1, the following mixtures were formed into tablets:

Disopyramid. phosphate	257.6 mg
Eudragit E 30 D	110 mg
Cutina HR	10 to 40 mg (3.3 to 12.1%)
Lithium sulphate (crystalline)	384 mg
Eudragit E 30 D	150 mg
Cutina HR	up to 20 mg (up to 4.5%) provided that the content of Cutina HR is never zero
Verapamil. chloride	100 mg
Eudragit E 30 D	80 mg
Cutina HR	2.5 to 10 mg (2 to 7.5%)
Phenylpropanolamine chloride	50 mg
Calcium phosphate	120 mg
Eudragit E 30 D	80 mg
Cutina HR	40 mg (2.4%)

It was ascertained that the dissolution was practically in direct proportion to the quantity of the Cutina HR used as the controlling agent and independent from the compression pressure.

Example 2

Metformine tablets

Metformine hydrochloride	500 mg
Cutina HR	50 mg
Eudragit RS	70 mg
Methylenechloride	105 mg
Cutina HR	q.s.

The metformine hydrochloride and the Cutina HR, which was used here partly already in the granulation in order to prevent adherence of the mix to the machines, were mixed together.

The mixture was moistened with Eudragit RS-methylenechloride solution and dried.

The dry mix was screened, and the Cutina HR used as the controller of liberation was mixed into the grains obtained in this way.

The dissolution of the active agent into water during 1 hour was determined from the tablets as a function of the quantity of the controlling agent (Cutina HR). A linear relationship was found as shown in Fig. 3 of the accompanying drawings.

In the second experiment the compression of the tablets was performed from the same mixture with different compression pressures, whereupon the dissolution of the active agent during 1 hour was determined as described above. The result is shown in Fig. 4 of the accompanying drawings.

In an analogous way, by using a methylenechloride solution of polymethacrylate, tablets of the following compositions were prepared:

Potassium chloride	500 mg
Eudragit RS	70 mg
Cutina HR	45 mg (6.5%)
Potassium chloride	750 mg
Eudragit RS	100 mg
Cutina HR	30 mg (3.1%)
Anhydrous ferrous sulphate	272 mg
Eudragit RS	20 mg
Eudragit S 12.5	60 mg
Cutina HR	15 mg (3.6%)

As in the above cases, it was also in this case ascertained that the dissolution was in almost direct proportion to the quantity of the Cutina HR

used as the controlling agent and independent from the compression pressure.

Claims

1. A process for the preparation of matrix-type tablets with controlled liberation of the active agent, characterized in that the retarding matrix substance used in the granulation process comprises at least 8.75 wt.%, based on the gross weight of the tablets, of a methacrylate polymer, insoluble in neutral or slightly acid water either in solution in an organic solvent or as a dispersion In water and that, before the tablets are compressed, an ester of a high molecular weight fatty acid or a derivative thereof produced by hydrogenation is mixed into the grain mix as a controlling agent in an amount (within the range 1-30% by weight based on the gross tablet weight) calculated to provide a determined rate of release of the active agent which is independent of the tablet compression pressure.

2. A process as claimed in Claim 1 characterized in that a copolymerizate of acrylic and methacrylic acid esters containing quarternary ammonium groups, or a copolymerizate of methacrylic acid and methyl ester of methacrylic acid with anionic character is used as the retarding matrix substance.

3. A process as claimed in Claim 1, characterized in that a water dispersion of a copolymerizate of methyl and ethyl esters of acrylic and methacrylic acid with neutral character is used as the retarding matrix substance.

4. A process according to any preceding claim characterized in that as the controller agent for the rate of the active agent is used hydrogenated castor oil or hydrogenated cotton seed oil.

5. A process according to any preceding claim wherein the said controlling agent is selected from glycerides of acids of formula CH_3—$(CH_2)_{9-22}$—COOH, and CH_3—$(CH_2)_{9-29}$—OH esters of the same acids.

6. A process according to any one of Claims 1 to 4, characterized in that the quantity of the controlling agent is not more than 30 wt.% based on the gross weight of the tablets.

7. A process according to Claim 5 characterized in that the quantity of the controlling agent is not more than 15 wt.% based on the gross weight of the tablets.

8. A process according to any preceding claim characterized in that the methacrylate polymer content is 8.6 to 21.8 wt.%, based on the total composition.

9. Matrix-type tablets made by a process according to any preceding claim.

Patentansprüche

1. Ein Verfahren zur Herstellung von Tabletten d s Matrixtyps mit gest uerter Freisetzung des Wirkstoffs, dudurch gekennzeichnet, daß die im Granuli rungsverfahr n ingesetzte verzög rnde Matrixsubstanz wenigstens 8,75 Gew.-%, bezogen auf das Bruttogewicht der Tabletten, eines in neutralem oder schwach saurem Wasser unlöslichen Methacrylatpolymers, entweder in einem organischen Lösungsmittel gelöst od r als Dispersion in Wasser, umfaßt und daß vor dem Pressen der Tabletten ein Est r einer Fettsäure von hohem Molekulargewicht oder ein durch Hydrierung gebildetes Derivat davon in das Granulierungsgemisch als Steuerungsmittel in einer Menge (innerhalb des Bereiches von 1—30 Gew.-% bezogen auf das Bruttogewicht der Tabletten) gemischt wird, der berechnet ist, um eine vorgegebene Freisetzungsrate des Wirkstoffs zu ergeben, die unabhängig vom Tablettenpreßdruck ist.

2. Ein Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß ein Copolymerisat von Acryl- und Methacrylsäureestem, die quaternäre Ammoniumgruppen enthalten, oder ein Copolmerisat von Methacrylsäure und dem Methylester von Methacrylsäure mit anionischem Charakter als verzögernde Matrixsubstanz verwendet wird.

3. Ein Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß eine Wasserdispersion eines Copolymerisates von Methyl- und Äthylestern von Acryl- und Methacrylsäure mit neutralem Charakter als verzögernde Matrixsubstanz verwendet wird.

4. Ein Verfahren nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß als Steuerungsmittel für die Freisetzungsrate des Wirkstoffes hydriertes Rizinusöl oder hydriertes Baumwollsamenöl verwendet wird.

5. Ein Verfahren nach einem der vorhergehenden Ansprüche, worin das genannte Steuerungsmittel aus Glyzeriden von Säuren der Formel CH_3—$(CH_2)_{9-22}$—COOH, und CH_3—$(CH_2)_{9-29}$—OH estern der gleichen Säuren ausgewählt wird.

6. Ein Verfahren nach einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, daß die Menge an Steuerungsmittel nicht mehr als 30 Gew.-%, bezogen auf das Bruttogewicht der Tabletten, beträgt.

7. Ein Verfahren nach Anspruch 5, dadurch gekennzeichnet, daß die Menge an Steuerungsmittel nicht mehr als 15 Gew.-%, bezogen auf das Bruttogewicht der Tabletten, beträgt.

8. Ein Verfahren nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß der Gehalt an Methacrylatpolymer 8,6—21,8 Gew.-%, bezogen auf die gesamte Zusammensetzung, beträgt.

9. Tabletten des Matrixtyps, hergestellt nach einem Verfahren nach einem der vorhergehenden Ansprüche.

Revendications

1. Procédé de fabrication de comprimés du type à matrice avec libération controlée de l'agent actif, caractérisé en ce que la substanc formant la matric r tardatrice utilisée dans le procédé de granulation compr nd au moins 8,75% en poides par rapport au polds brut des comprimés dans de

l'eau neutr ou légèrement acide, soit en solution dans un solvant organique soit sous forme d'une dispersion dans l'eau et que, avant la compression des comprimés, un ester d'un acide gras de haut poids moléculaire ou un dérivé de celui-ci produit par hydrogénation, est mélangé au mélange de graines en tant qu'agent de contrôle, en une qunatité (dans la gamme de 1 à 30% en poids par rapport au poids brut des comprimés) calculée façon à assurer une libération de l'agent actif à une vitesse prédéterminée qui est indépendante de la pression d'empastillage.

2. Procédé selon la revendication 1, caractérisé en ce qu'un copolymérisat d'esters acrylique et méthacrylique contenant des groupes ammonium quaternaire, ou un copolymérisat d'acide méthacrylique et de méthacrylate de méthyle de caractère anionique, est utilisé en tant que substance formant une matrice retardatrice.

3. Procédé selon la revendication 1, caractérisé en ce qu'une dispersion aqueuse d'un copolymérisat d'esters méthylique et éthylique d'acide acrylique et d'acide méthacrylique ayant un caractère neutre, est utilisé comme substance formant une matrice retardatrice.

4. Procédé selon l'une quelconque des revendications précédentes, caractérisé en ce que l'agent contrôlant la libération de l'agent actif utilisé, est une huile de ricin hydrogénée ou une huil de graines de coton hydr génée.

5. Procédé s lon l'une quelconque des revendications précédentes, caractérisé en ce que cet agent de contrôle est choisi parmi des glycérides d'acides de formule $CH_3—(CH_2)_{9-22}—COOH$ et des esters de $CH_3—(CH_2)_{9-29}—OH$ formés avec les mêmes acides.

6. Procédé selon l'une quelconque des revendications 1 à 4, caractérisé en ce que la quantité d'agent de contrôle ne dépasse pas 30% en poids par rapport au poids brut des comprimés.

7. Procédé selon la revendication 5, caractérisé en ce que la quantité d'agent de contrôle ne dépasse pas 15% en poids par rapport au poids brut des comprimés.

8. Procédé selon l'une quelconque des revendications précédentes, caractérisé en ce que la teneur en polymère méthacrylique est de 8,6 à 21,8% en poids par rapport à la composition totale.

9. Comprimés du type à matrice, fabriqués conformément à un procédé selon l'une quelconque des revendications précédentes.

FIG.1

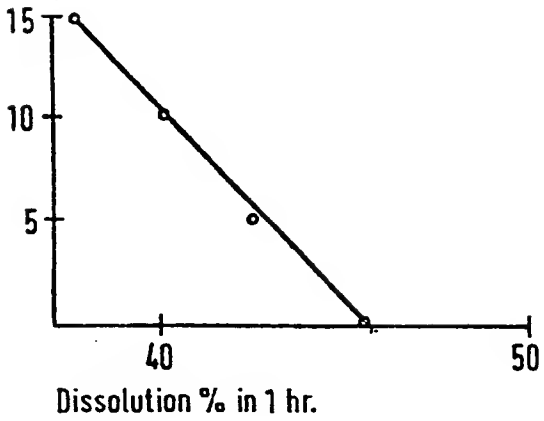

FIG.2

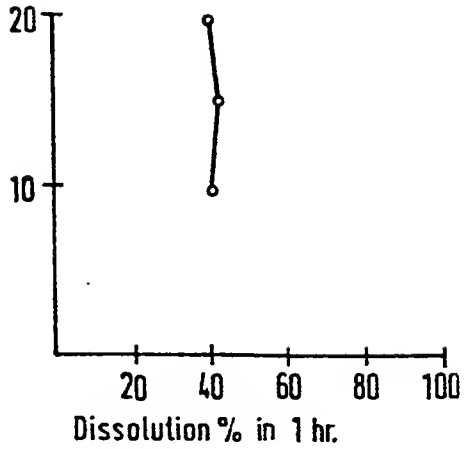

FIG.3

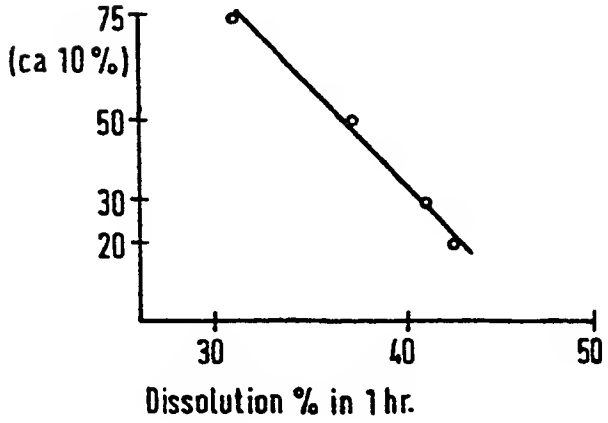

FIG.4